PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing *(day/month/year)* **04 FEBRUARY 2005 (04.02.2005)**

Applicant's or agent's file reference
JL-23356-PCT

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/KR2004/002770	**30 OCTOBER 2004 (30.10.2004)**	30 OCTOBER 2003 (30.10.2003)

International Patent Classification (IPC) or both national classification and IPC
IPC7 C07D 501/22

Applicant
CJ CORPORATION et al

1. This opinion contains indications relating to the following items:

- [X] Box No. I Basis of the opinion
- [ ] Box No. II Priority
- [ ] Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- [ ] Box No. IV Lack of unity of invention
- [X] Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- [ ] Box No. VI Certain documents cited
- [ ] Box No. VII Certain defects in the international application
- [ ] Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**
If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.
For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/KR
Korean Intellectual Property Office
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Republic of Korea
Facsimile No. 82-42-472-7140

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Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material
   - ☐ a sequence listing
   - ☐ table(s) related to the sequence listing

   b. format of material
   - ☐ in wirtten format
   - ☐ in computer readable form

   c. time of filing/furnishing
   - ☐ contained in the international application as filed.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additioanl copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

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Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-16	YES
	Claims		NO
Inventive step (IS)	Claims	1-16	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-16	YES
	Claims		NO

2. Citations and explanations :

Reference is made to the following documents:

D1 : WO 02/68428 A1

D2 : US 4708825

D3 : US 4463179

D4 : US 4223134

D5 : WO 02/83692 A1

D6 : US 5171854

D1 discloses a preparation method of cephalosporin which comprises reacting a cephem compound with a 4-hydroxyphenylglycine whose carboxylic group is activated by pivaloyl chloride or disuccinamidyl carbonate.

D2 discloses a method for producing cephalosporin antibiotics which involves reacting a 7-aminocephalosporin derivative with phenylglycyl chloride hydrochlorides obtained by reaction of N-substituted phenylglycines with thionyl chloride and the gaseous hydrochloride.

D3 discloses thiol esters of 4-hydroxyphenylglycine effective as acylating agents for amines of 7-aminocephalosporin derivative.

D4 discloses silyated and enamine protected 4-hydroxyphenylglycine sodium salt useful for the acylation of cephalosporin nuclei.

D5 discloses that 3-(Z)-propenyl cephem compound is selectively prepared by reacting a phosphoranylidene cephem compound with acetaldehyde in the presence of base in a solvent mixture essentially comprising diethyl ether.

D6 discloses a method of raising the Z- to E-isomer ratio in a 3-propenyl cephem compound by conducting Wittig reaction in the presence of lithium halide.

(Continued on Supplemental Sheet.)

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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of :

1.Novelty and Inventive Step
(1) Concerning claims 1-6
Claims 1-6 relate to a method of preparing cephalosporin antibiotics which comprises reacting a cephem compound of formula (3) with 4-hydroxyphenylglycine derivative of formula (2) in the presence of base. None of the prior art uses the 4-hydroxyphenylglycine derivative of formula (2) for the acylation of cephem compound, which is not considered obvious to a person skilled in the art. Moreover, the process of the present invention has an advantage to be carried out in a one-pot reaction.
Therefore, claims 1-6 of the present invention are considered to meet the requirements of Articles 33(2) and 33(3) PCT.

(2) Concerning claims 7-14
Claims 7-14 relate to a 4-hydroxyphenylglycine derivative of formula (2) and the preparation method thereof.
None of the prior art discloses the triphenylphosphorane salt derivative of 4-hydroxyphenylglycine as an activated derivative of 4-hydroxyphenylglycine for acylation reaction, whose structure is not related with the derivative of 4-hydroxyphenylglycine disclosed in the prior art.
Therefore, claims 7-14 of the present invention are considered to meet the requirement of Article 33(2) and 33(3) PCT.

(3) Concerning claims 15-16
Claims 15-16 relate to a method of preparing 3-(Z)-propenyl cephem compound of formula (3a) comprising reacting phosphoranylidene cephem compound of formula (5) with acetaldehyde in the presence of base in a solvent mixture comprising water, isopropanol and methylene chloride in the ratio of 1 : 3~6 : 11~14.
None of the prior art suggests the solvent system for raising the Z- to E-isomer ratio in 3-propenyl cephem compound.
For the analysis of the inventive step, D5 is considered the closest prior art. D5 suggests a two-phase solvent system, and the organic phase thereof essentially comprising a diethyl ether for raising the Z-isomer content. Also, D5 describes that it is difficult to raise the Z-isomer content to above 83% when Wittig reaction is conducted using a conventional organic solvent such as methylene chloride.
From the disclosure of D5, the solvent system of the present invention is not obvious to a skilled person in the art.
Therefore, claims 15-16 of the present invention are considered to meet the requirement of Article 33(2) and 33(3) PCT.

2. Industrial applicability
Claims 1-16 have industrial applicability.